UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/217,324	03/24/94	OSBORNE	W 163363

EXAMINER	
NEWELL, M	
ART UNIT	**PAPER NUMBER**
1804	6

18M2/1002

STEVEN W. PARMELEE
TOWNSEND AND TOWNSEND KHOURIE AND CREW
STEUART STREET TOWER
ONE MARKET PLAZA
SAN FRANCISCO, CA 94105

DATE MAILED: 10/02/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-22 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1-22 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and use the invention and failing to provide an enabling disclosure. Applicant's claims are broadly directed to devices and methods for the implantation of genetically modified cells into the vascular system of a human (or animal) "patient" for therapeutic purposes. The invention as claimed encompasses the implantation of smooth muscle cells expressing any "gene of interest" into any animal such that a recombinantly expressed gene product can be delivered as a therapeutic. This is further elaborated in the specification to include "enzymes, cytokines, receptors, hormones, growth factors, coagulation factors, and the like" (page 4, lines 30-32). There is insufficient guidance in the specification for a skilled artisan to recombinantly express in vivo such a gene encoding one of these products for therapeutic use, at a therapeutic level, with proper regulation of expression.

This position is taken for the following reasons. Claim 19, for example, is drawn to "a method for treating or preventing diabetes in a patient" using a vascular graft seeded with smooth

muscle cells that "constitutively express an insulin or proinsulin polypeptide". There is no information in the specification that would guide one of ~~ordinary skill~~ skill in the art to transduce the insulin or proinsulin gene into appropriate target cells such that the level of expression necessary to treat the disease would be sufficient as a treatment. No information is provided regarding the regulation of insulin expression in response to physiological signals. In addition, this diabetes treatment would not be applicable to patients whose disease is attributable to a lack of insulin receptor molecules rather than insufficient insulin secretion. The treatment of anemia by implantation of erythropoietin-expressing cells is an analogous example of a genetic treatment dependent on tight regulation of gene expression.

The working example in the specification as filed describes the transfer of the lacZ gene, which does not code for a therapeutic compound, and the PNP (purine nucleotide phosphorylase) gene, which does not require precisely regulated expression for therapeutic use. No long-term study data is presented to show the existence or duration of therapeutic levels of protein production. The transduction and expression of the lacZ gene in the animal model presented is not correlatable to the transduction and expression of a therapeutic gene. A skilled artisan would not be inclined to accept short-term expression of a non-therapeutic gene at an undefined expression level as

evidence that the claimed invention can treat a diseased patient with a reasonable expectation of success. Likewise, transduction and short-term expression of the PNP gene is not sufficient evidence to convince a skilled artisan that the invention can be successfully used to supply a therapeutic level of a secreted product (such as erythropoietin) or a product requiring strict regulation (such as insulin).

In the invention as claimed, the cells may be transduced by any method, including retroviral, adenoviral and non-viral systems. In the working examples, autologous smooth muscle cells are transduced by a retroviral vector. There are characteristics of each vector system that would contribute to the unpredictability of using the claimed invention as well as limiting its therapeutic utility. The insert size of retroviral vectors is limited to about 8kb, making the retroviral expression of a large gene (such as Factor VIII) impossible with a retroviral system. Further evidence of the unpredictable nature of recombinant delivery of therapeutic genes is taught by Jolly, who teaches that "it is worth noting that building retroviral vectors is still a mixture of art and science. Many creative ideas require multiple design attempts before performing anywhere close to desired" (page 53). Of import to applications where regulated expression is necessary, Jolly adds that "tissue-specific promoters can be successfully incorporated into vectors, but in our experience about one of five alternative designs will

behave satisfactorily. It has gradually become apparent that, in general, as the complexity of design increases, the corresponding vector titers usually (but not always) decrease" (page 53). Anderson (Human Gene Therapy, Volume 5, pages 281-282) also addresses this limitation, writing on page 281 that

> Unfortunately, we are still woefully ignorant of the regulatory mechanisms that control gene expression in primary cells in vivo. Vectors for gene therapy are, to a certain extent, hit or miss. Viral promoters work well in culture so that many vectors are made using the viral vector's own promoters or are made with SV-40, CMV, or other viral regulatory sequences. Unfortunately, we know that many viral promoters are shut off in primary cells in vivo, but studies using human regulatory sequences are very preliminary.

Other considerations for the use of retroviral vectors include transcriptional shut-off, leading to short term in vivo expression, generally low expression levels (compared to adenoviral systems, for example), and the possibility of insertional mutagenesis leading to tumorigenesis. Adenoviral vectors provide high expression levels but duration is limited (2-6 weeks); they have the additional limitation of inducing a strong immune response that results in inflammation and reaction against repeated administrations. Non-viral systems are limited by transduction efficiency and the inability to integrate into the genome, resulting in transient gene expression. Since long-term, high level expression is necessary for the claimed invention to be therapeutically successful, guidance must be

presented to allow one of ordinary skill to choose and evaluate vector constructs in light of the parameters described above.

The working example presented results of the transduction of smooth muscle cells obtained from a baboon, their seeding (with endothelial cells) on a synthetic graft, and the implantation of the graft into the vascular system of the animal. The invention as claimed is directed to the treatment of disease in any animal, including human beings, using the claimed devices and methods. Ledley et al. reviews somatic gene therapy, and states (on page 79) that

> While animal experiments are useful for assessing specific aspects of gene transfer, there is no data explicitly supporting the contention that animal experiments can presage the outcome, efficacy, or safety of human applications. The details of anatomy, cell biology, genetics, and immunology of other species do not duplicate the vicissitudes of human biology, particularly when considering retroviral vectors whose infectivity, tropism, and pathology is naturally species specific.

Of particular import are species differences in the efficiency of tissue culture, transduction and expression of human smooth muscle cells, compared to the results presented in the animal model. In addition, the animal experiments were conducted on a small sample size and were not directed toward treatment of disease. Therefore it is not likely that the animal studies presented would be accepted by the skilled artisan as support for the claimed subject matter.

The claimed invention encompasses the use of both natural and synthetic grafts to implant genetically modified cells in

vivo. These grafts have been shown in the art to be susceptible to atherosclerosis and occlusion over time in vivo. The long term patency of biologic venous grafts is "very much limited by accelerated graft atherosclerosis" (Mann et al., p.4502). Mann et al. also report (on page 4502) that

> It has been speculated that the seeding of artificial graft materials with genetically engineered endothelial cells might reduce their tendency for thrombosis when placed in these small and medium-sized vessels. To date, there has been no report of the successful development of such a graft.

Stanley et al. review vascular grafts and describe the following limitations: thrombogenicity of surfaces, deterioration of biologic grafts, and infectivity of synthetic prostheses. They further describe the ideal vascular prosthesis as "biocompatible, nonthrombogenic, physically durable while mimicking the elastic compliance properties of the vessel within which it is implanted, resistant to infection, and technically easy for the surgeon to implant" (page 365). In the working example presented by the Applicant, grafts are removed and examined after 3-5 weeks (Specification, page 16). Applicant reported no flow-limiting stenosis after this limited time period. Applicant provides no evidence of long-term patency of the invention as claimed, and provides insufficient guidance for one of ordinary skill to choose both the proper graft material for specific applications, as well as steps in the claimed method that would limit thrombosis and atherosclerosis.

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art to practice the invention.

Claims 1-22 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-4, 8-11, 13, and 16-20 are rejected under 35 U.S.C. § 103 as being unpatentable over Noishiki et al.(U.S. 5,387,236) in view of Nabel et al.(U.S. 5,328,470).

The claimed invention is drawn to a vascular graft seeded with transduced smooth muscle cells that express a therapeutic gene product, and the use of such a graft, implanted in the vasculature, to treat a patient in need of the therapeutic gene product. Noishiki discloses a vascular prosthesis in which autologous (page 2, lines 58-63) endothelial cells and smooth muscle cells are deposited. The cells adhere to and are captured within the wall of the prosthesis. The vascular graft disclosed by Noishiki may be synthetic, composed of PTFE, and may be coated with a polymer, for example, collagen (pages 2-3). The Noishiki reference differs from the claimed invention in that the cells deposited on the graft are not genetically modified to secrete therapeutic compounds for the treatment of disease.

The Nabel reference discloses the in situ transduction of endothelial and smooth muscle cells of the arterial wall, or the deposition of cells transduced ex vivo, using a catheter to deposit the cells or appropriate gene transfer vehicle (pages 6-8, see "II: Introduction of cells expressing normal or exogenous proteins into the vasculature"). Nabel discloses the use of the invention to deliver insulin (page 5, line 30), or anticoagulant factors such as urokinase (page 11, line 46-49). Nabel thus discloses in situ gene transduction of smooth muscle cells for therapeutic benefit, but does not disclose a vascular graft containing transduced smooth muscle cells as the method of delivering the gene product of interest.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a synthetic vascular graft to transplant endothelial and smooth muscle cells into a blood vessel as disclosed by Noishiki, and to substitute genetically modified for unmodified cells, based on the teaching of the Nabel reference to genetically modify cells of the arterial wall for therapeutic purposes.

Claims 5-7 and 12-15 are rejected under 35 U.S.C. § 103 as being unpatentable over Noishiki et al. in view of Nabel et al., as applied to claims 1-4, 9-11, 13 and 16-20 above, and further in view of Anderson et al.(WO 90/224,525).

Anderson discloses a vascular graft coated with genetically-modified autologous endothelial cells, and further discloses the use of this invention to deliver erythropoietin, Factor IX, G-CSF and GM-CSF proteins, among others. Anderson does not disclose the inclusion of transduced vascular smooth muscle cells in the graft, which would be obvious to one of ordinary skill in the art based on the Noishiki reference, which includes smooth muscle cells in its graft, and the Nabel reference, which teaches the desirability of vascular smooth muscle cells as a target for gene therapy.

Claims 21 and 22 are rejected under 35 U.S.C. § 103 as being unpatentable over Noishiki et al. in view of Nabel et al., as applied to claims 1-4, 9-11, 13 and 16-20 above, and further in view of Bell et al.(U.S. 5,336,615).

Bell discloses genetically engineered endothelial cells (bovine calf aortic endothelial cells in Example 1) that are grown in autologous serum (fetal bovine) before seeding either denuded vessel segments or natural or synthetic grafts. It is well known in the art to adjust tissue culture parameters such as serum source and concentration, temperature or CO_2 concentration to optimize cell growth. It would be obvious to one of ordinary skill in the art to use the example of Bell and culture cells for gene therapy procedures in autologous serum, in an effort to improve cell growth and viability.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Newell whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday to Friday from 8:30 AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached on (703) 308-3153. The fax phone number for this Group is (703)308-4213.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)308-0196.

Michael Newell

July 24, 1995

JOHN L. LeGUYADER
PATENT EXAMINER
GROUP 1800